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(54) Title: COMPOUNDS FOR USE IN MEDICINE

(57) Abstract: A compound for use as an active pharmaceutical substance comprising a halogen compound.

DESCRIPTION

COMPOUNDS FOR USE IN MEDICINE

The present invention relates to a compound for use in medicine, more particularly it relates to a compound for use as an active pharmaceutical substance and the use of a compound for the manufacture of a medicament for the treatment of cancers and other conditions where the use of an antioxidant or oxidising agents leads to an improvement in the condition. Such conditions include, but are not limited to, lung cancer, testicular tumours, leukemias, sarcomas lymphomas and conditions caused by pathogens such as bacteria. Oxidative killing is important in the killing of organisms, in particular those associated with bacterial infections such as staphylococci which are commonly responsible for surgical infections. Oxidative killing consumes and requires molecular oxygen which it converts to superoxide anion. In this process a membrane bound NADPH oxidase is activated and a burst of respiration follows. Part of the consumed oxygen is converted to a series of oxygen radicals including superoxide, hydroxyl radical and hypocholoride which are released into phagosomes and assist in bacterial killing. The act of oxidizing or state of being oxidised chemically consists in the increase of positive charges in an atom or the loss of negative charges. Most biological oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidation must be accompanied by reduction from an acceptor molecule.

In most Western countries cancer is the second most prevalent cause of death after heart disease and accounts for 20-25% of all deaths.

Whilst in most cases the causes of cancer remain unknown, rapid advances in the last few decades in understanding the difference between cancer cells and normal cells at the genetic level has resulted in the widely accepted understanding that cancer results from acquired changes in the genetic make-up of a particular cell or group of cells which give rise to a failure of the normal mechanism regulating their growth.

Cancer is what happens when a group of cells grows uncontrollably and in an abnormal and disorderly way. It is really a result of what happens when the normal growth mechanism fail for reasons that we only partly understand. Cancer cells have two properties that make them dangerous. Then can invade into neighbouring tissues and they can spread to distant areas of the body, forming secondary tumours of metastases.

Cigarettes for example cause 95% of cancer of the lung as well as being a major factor in cancers of the bladder, pancreas, mouth, oesphagas and kidney. Cancer cells can multiply to produce literally billions of cells before a tumour becomes big enough to detect.

Other environmental factors known to give rise to cancer, such as radiation, chemicals, such as asbestos, and free radicals, do so by increasing the overall rate of acquired genetic damage.

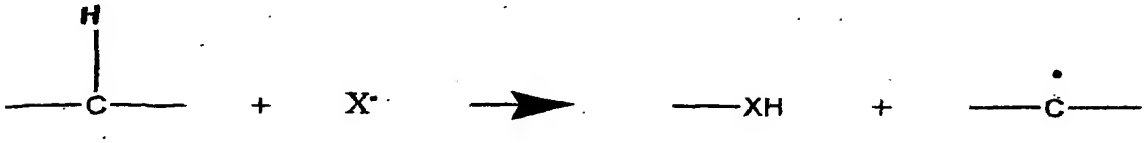
Free radical mediated damage is another cause of endogenous genetic toxicity. Free radicals are highly reactive atoms or molecular which are produced by normal oxidative metabolism during a variety of pathological processes, including

inflammation, tissue reperfusion after vascular blockage and damage by UV light and ionising radiation.

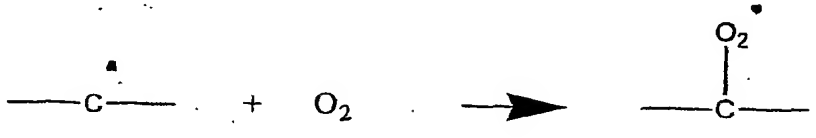
Free radicals can damage proteins, lipids, DNA and other molecules by oxidation. Individual free radicals vary considerably in their reactivity and half life in biological systems. The hydroxyl radical is the most reactive, degrading any molecule within diffusion distance and is considered to be the ultimate radical species responsible for DNA damage.

Thymine oxidation products have been detected in human urine and appear to result from the removal of oxidised DNA bases during DNA repair. It has been estimated that each human cell undergoes between 10^3 and 10^4 oxidative modifications to the Thymine in its DNA each day. There is evidence to suggest that this oxidative damage is involved in some of the events of cancer induction and progress.

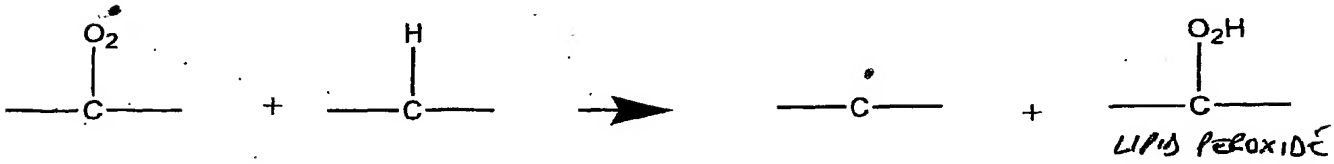
Lipid peroxidation occurs when a reactive radical (such as NO_2, OH, or CCl, O_2) abstracts an atom of hydrogen from polyunsaturated fatty-acid side-chain in membrane or lipoprotein. This leaves unpaired electron on carbon (hydrogen atom has only one electron, so its removal must leave spare electron):



Carbon radical reacts with oxygen:



Resulting peroxyl radical attacks adjacent fatty-acid side-chain to generate new carbon radical:



And chain reaction continues:

Overall, attack of one reactive free radical can oxidise multiple fatty-acid side-chains to lipid peroxides, damaging membrane proteins, making the membrane leaky, and eventually causing complete membrane breakdown.

Despite all antioxidants some free radicals still escape to subsequently do damage. Thus DNA undergoes constant -"oxidative damage" and has to be repaired. Free radical-damaged proteins are degraded and the end products of Lipid peroxidation (eg the isoprostanes) and of free radical attack on urate are present in vivo.

Because antioxidant defences are not completely efficient increased free-radical formation in the body is likely to increase damage.

The term "oxidative stress" is often used to refer to this effect. If oxidative stress occurs tissues often respond by making extra antioxidant defences. However severe oxidative stress can cause cell injury and death.

Many cancers can be cured by surgical removal if they are detected early enough, before there has been spread of significant numbers of tumour cells to other

parts of the body, and if they are readily accessible.

If complete surgical removal of the tumour is not possible, then partial removal by surgery and/or radiotherapy or chemotherapy is usually employed. Certain tumours are highly sensitive to chemotherapy and may be cured by the use of chemotherapeutic drugs alone.

Numerous methods have been used to try to cure and/or treat cancer, for example, the use of hydrazine sulphate or intravenous injection of large amounts of vitamin C as antioxidants.

Although higher dietary intakes of antioxidant nutrients β carotene, vitamin C and vitamin E are associated with a lower risk of cancers, including oesophageal cancer, in case control studies the results from intervention trials have not demonstrated any effect on either the prevalence or pre-cancerous lesions or on the incidence and mortality of cancers such as oesophageal cancer. It is possible that the apparent effect observed in epidemiological studies is due to confounding by other factors for example smoking. Consequently, evidence to suggest that vitamins A, C, E or Beta Carotene protect against the development of cancers is inconclusive.

Higher intakes of the antioxidant vitamins A, C, E and β carotene have been variously associated with lower risks of breast, colrectal, lung, gastric and cervical cancer in case control and prospective studies.

Most of the intervention trials that have been caused to have been carried out so far with supplements of these vitamins have failed to confirm a hypothesised protective effect of these vitamins on cancer.

In accordance with a first aspect of the present invention there is provided a compound for use as an active pharmaceutical substance comprising a halogen compound.

The halogen compound may comprise at least one atom selected from the group comprising F, Cl, Br and I. Fluorine is the most reactive (the best oxidising agent) and Iodine the least.

Preferably, the compound comprises at least one I, Cl or Br atom. More preferably, the compound comprises at least one I or Br atom. More preferably still, the compound comprises at least one I atom, since I enters organic molecules more readily than F, Br or Cl by direct addition at double bonds and by displacement of hydrogen.

Preferably the compound comprises at least two halogen atoms. More preferably the halogen compound is obtained by the direct combination of at least two halogens.

The halogen compound may be solid or liquid.

The halogen compound may be any one selected from the group ICl, IBr, ICl_3, IF_7, IF_5 or BrF_3.

Preferably the compound is ICl.

Positively charged iodine can be produced, for example, using iodine monochloride and reducing this compound by the addition of potassium iodide in a mixture of acetic acid and carbon tetrachloride (WIJS reagent, British Standard BS684 section 2.13..1981 ISO 3961 - 1979 para 6.6). The positively charged iodine

liberated can then saturate double bonds in the molecules of the body requiring treatment and function as an antioxidant (Iodine Value AOCS Official Method Col 1-25, 1993) . Furthermore, positively charged Bromine and Fluorine can be produced by a similar method

The compounds may be administered orally, intravenously, subcutaneously or by any other route. For oral application, the compounds can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release ore timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions.

The dosage requirement utilising the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the particular compound employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the compound required to prevent, counter or arrest the progress of the condition.

The adult dosage may, for intravenous application, range from 1050 mg to 1400 mg weekly.

The preferred weekly dose is from 15 to 20 mg per Kg of body weight. Thus for a 70Kg adult, the weekly dose can range from 1050 mg to 1400 mg. This weekly dose may be administered in divided doses from 1 to 7 times a week giving unit doses for an adult of from 150 to 1400 mg.

The compounds can form the active ingredient, and are typically administered

in admixture with suitable pharmaceutical diluents, excipients or carriers suitably selected with respect to the intended form of administration.

The compounds may be administered with a reducing agent. Preferably, the reducing agent comprises an electropositive metal, such as sodium. More preferably the reducing agent is hydrazine sulphate.

The compounds may be administered by any means that treat and/or prevent conditions where an antioxidant or an oxidising agent are effective in treating or preventing the condition. Such conditions include cancers and bacterial infections.

Compounds of the present invention may be useful for treating and/or preventing conditions prevalent in humans and animals. **In particular, the compounds may be usefule for treating and/or preventing MRSA, Parkinson's disease, Alzheimer's disease, Hodgkin's disease, BSE (Bovine Spongiform Encelphalophathy), CJD (Creutzfeldt-Jakob disease), Foot and mouth disease, AIDS, Multiple Sclerosis, heart conditions, atheroscleorsis, colitis, malaria, all sexually transmitted diseases, including gonorrhoea and syphilis, herpes, sclerosis, all kinds of skin conditions and may be used in all kinds of sexual stimulants and aphrodisiacs and for impotence, and other conditions and diseases.**

In accordance with a second aspect of the present invention, there is provided the use of a halogen compound for the manufacture of a medicament for the treatment of cancers.

The invention will be further described, by way of example only, with

reference to the following compositions.

Brominated vegetable oil.

The food additive brominated vegetable oil may be safely used in accordance with the following prescribed conditions:

(a) The additive compiles with specifications prescribed in the Food Chemicals Codex 3d Ed, (1981), pp. 40-41, except that free fatty acids (as oelic) shall not exceed 2.5 percent and Iodine value shall not exceed 16. Copies of the material incorporated by reference may be obtained from the National Academy Press, 2101 Constitution Av, NW, Washington, DC 20418, or may be examined at the Office of the Federation Register, 800 North Capital Street, NW Suite 700, Washington DC 20418.

(b) The additive is used on an interim basis as a stabilizer for flavouring oil used in fruit-flavoured beverages for which any applicable standards of identity do not preclude such use, in an amount not to exceed 16 parts per million in the finished beverage, pending the outcome of additional toxicological studies on which periodic reports at 6 month intervals are to be furnished and final results submitted to the Food and Drug Administration promptly after completion of the studies.

Halogenation of unsaturated oils generally leads to agents which have low toxicity. This is further illustrated by Brominated oil. Brominated oil has been used as a clouding agent in fruit drinks. It is produced by bromination of unsaturated oils and its yellow colour, bland taste, and neutral buoyancy are

used to enhance the appearance of fruit juices including orange juice. (see above).

Brominated oils can be obtained from Dominion Products Incorporated, 882 3rd Avenue, Brooklyn New York, USA; or

Penta Manufacturing Co, 50 Okner Parkway, Livingston, New Jersey, USA.

Iodised Oil

Iodised oil is the subject of a monograph in the 1998 British Pharmacopoeia and USP23. Iodised oil (also known as ethiodised oil) is an addition product of the ethyl esters of the unsaturated fatty acids and may be obtained from poppy seed oil obtained from A and E CONNOCK. (Perfumery and Cosmetics Ltd), Alderholt Mill House, Fordingbridge, Hampshire, SP6 1PU UK. It contains 35-39% of combined iodine. Iodised oil may be given by injection. Other unsaturated oils include sunflower oil, olive oil, palm oil, soya bean oil, rape oil maize oil, flax seed oil and the like. Unsaturated chemicals include the fatty acids such as stearic acid and oleic acid.

Potassium Iodide is the subject of a monograph in the British Pharmacopoeia and also in other European and American Pharmacopoeias.

An aqueus iodine solution can be made as follows. 5 grams of iodine are added to 100 ml of water. Added to this is 10% of Potassium Iodide to make the iodine dissolve. A desired dosage of this preparation as disclosed hereinabove can be given 3 times a day for a short time.

Substituting Fluorine in some compounds and the consequences can be dramatic and important. Vinegar, CH_3COOH, for example having a Fluorine atom inserted CH_2FCOOH, gives rise to one of only a handful of fluorine containing compounds found in nature.

Selectively fluorinated products including F and CF_3 substituents can improve lipophilicity and suppress metabolic detoxification processes.

Very important antibacterial agents based on 6 fluoroquinolines and linezolid represent a new class of antibiotics.

Selective fluorinated molecules can enter biological systems. A single fluorine atom or a trifluoromethyl group can be attached to an aromatic ring within an active molecule. The presence of even a single fluorine atom in a molecule can totally change the outcome of what on paper appears to be a simple chemical transformation.

Examples of Fluorine compounds are Sodium Monofluorophosphate 0.75% w/w and sodium fluoride 0.01% w/w (Total fluoride 1050 ppm)

Halogens can be included in soap perfumes and cosmetics to benefit the preparation as follows.

(eg) (1) A Sun burn cream

Nonionic emulsifier 100

Sunscreen agent 50

Mineral oil (cosmetic quality) 30

Cetyl alcohol 20

(2) A pearly vanishing cream

Stearic acid 200

Curd soap 50

water 800

(3) A perfume (medicated and Antiseptic)

50 Thyme oil 80 Rosemary oil

100 Cassia oil 200 lavender oil

100 clove oil 200 lemon oil

50 Eucalyptus oil

200 Rose geranium oil

20 Vetivert oil

Total 1000

Cosmetics are made by the catalytic action of hydrogen with such oils as castor, Palm Kernel, Cotton seed, sesame coconut, Soya bean, ground nut and fish oils.

(4) Soap.

100 Benzyl acetate

150 Rosewood

50 Ceraniol Java

200 Cedarwood

50 Cananga

50 Benzyl iso-eugenol

300 Ionoue

30 Musk xylene

70 Santol

Total 1000

(5) Halogen compositions as described hereinabove can be included in food preparations such as butter and margarine and biscuits. Hydrogenated oils are widely used in their manufacture.

CLAIMS

1. A compound for use as an active pharmaceutical substance comprising a halogen compound.

2. A compound as claimed in claim 1 comprising at least one atom selected from the group comprising F, Cl, Br and I.

3. A compound as claimed in claim 2 wherein the compound comprises at least one atom of I or Br.

4. A compound as claimed in claim 3 wherein the compound comprises at least one I atom.

5. A compound as claimed in any one of the preceding claims comprising two halogen atoms.

6. A compound as claimed in claim 5 wherein the compound is selected from the group comprising ICL, IBr, ICl_3, IF_7, IF_5, BrF_3.

7. A compound as claimed in any one of claims 1 to 5 wherein the halogen compound is potassium iodide or potassium bromide.

8. A compound as claimed in any one of the previous claims wherein the compound is in admixture with a suitable pharmaceutical diluent, excipient or carrier.

9. A compound as claimed in claim 8 wherein the compound is in admixture with an unsaturated oil, fat or chemical.

10. A compound as claimed in claim 9 wherein the compound is in admixture with an unsaturated vegetable oil or mixed unsaturated vegetable oil.

11. A compound as claimed in claim 9 or 10 comprising brominated oil and/or iodised oil.

12. A compound as claimed in any one of the previous claims wherein the compound is an oxidising agent or an antioxidant.

13. A compound as claimed in any previous claim for use in the prevention of lipid peroxidation.

14. A compound as claimed in any one of the previous claims for use in the manufacture of food preparations selected from the group comprising butter, margarines and biscuits.

15. A compound as claimed in any one of claims 1 to 13 for use in the treatment of cancer.

16. A compound as claimed in any one of the previous claims wherein the compound is for use in cosmetics, soaps or perfumes.

17. A compound for use as an active pharmaceutical substance comprising a halogen.

18. A compound as claimed in any one of the previous claims for use in the manufacture of a medicament for treating cancer.

19. A compound as claimed in any one of the previous claims wherein fluorine is present in a compound including the group CF, CF_2 or CF_3.

20. A compound as claimed in any previous claim wherein the halogen compound is a bacteriocide or an antibiotic.

21. A compound as claimed in any previous claim for use in any kind of chemotheropy.